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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/532,297	08/24/2005	Joseph Alexander Lasky	ON/4-32744A	1063

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EXAMINER	
THOMAS, TIMOTHY P	
ART UNIT	PAPER NUMBER
1614	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/532,297	LASKY, JOSEPH ALEXANDER	
	Examiner	Art Unit	
	TIMOTHY P. THOMAS	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 October 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,5,7 and 10* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,5,7 and 10* is/are rejected.

7)☒ Claim(s) *10* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Arguments

1. Applicants' arguments, filed 10/1/2008, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

2. Applicant's arguments with respect to the rejection under 35 USC 112, 1st paragraph have been fully considered but they are only persuasive in part:

Claims 10, 2, 5 and 7 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating pulmonary hypertension in the sense of the meaning of reduction of pulmonary hypertension in individuals with pulmonary hypertension, does not reasonably provide enablement for treating individuals in the sense of the meaning of prophylactic treatment.

The scope of enablement rejection has been modified to include instant claim 7, necessitated by the claim amendment to modify the dependence of this claim on claim 10. The scope of the enablement rejection has been modified so that the "curative" embodiment is no longer maintained as a basis for this rejection, but the "prevention" basis is maintained. The rejection basis for "prevention" is maintained for the reasons of record, and the reasons that follow.

Applicant argues the term "curative" is defined on p. 5 of the specification and conforms to what the Examiner has agreed is enabled — reduction of pulmonary

hypertension. This argument is persuasive for the following reason. It is noted that "treatment" is defined to mean "curative treatment" and "prophylactic treatment"; "curative" is defined to mean "efficacy in **treating** ongoing episodes of pulmonary hypertension". With treatment depending on curative and curative depending on treating, the definitions in the disclosure are circular, and somewhat unclear as to the precise meaning. However, for the purpose of this rejection, based on the definition provided for "curative", the meaning is taken as having efficacy with respect to episodes of pulmonary hypertension. This meaning is more consistent with the generally used term of "treatment" in the art, and does not have the same meaning as "cure"; on the contrary "curative" is considered to be aimed toward a "cure". The disclosed definition of "curative" is considered to be enabled, and therefore this embodiment within the meaning of "treating" is withdrawn as a basis for the instant enablement rejection.

Applicant argues that once a patient suffering from pulmonary hypertension has responded to the treatment it is reasonable to expect continuation of the treatment will prevent a new onset or recurrence of pulmonary hypertension, conforming to the definition of "prophylactic" on p. 5 of the specification. This argument is not persuasive for the reasons of record. "Prevention" is a more rigorous term than efficacy in treating ongoing episodes of pulmonary hypertension; prevention implies that neither a new onset or any recurrence of any episode of pulmonary hypertension will occur, not just that the severity of such an episode will be diminished, or that the onset of such an episode will be delayed. This more stringent requirement based on the meaning of the term "prevention" is not considered enabled, especially considering the uncertainty in

the state of the art relevant to the "prevention" embodiment presented in the record: i.e., that PAH is a disease with poor prognosis, more effective treatments need to be developed and unknown triggers contribute to the development of pulmonary hypertension. Accordingly, the embodiment within "treatment" of "prevention" is maintained to not be enabled.

3. Applicant's arguments with respect to the rejection under 35 USC 102 have been considered but are moot in view of the new ground(s) of rejection.

The previous rejection basis is withdrawn and the new ground of rejection is added necessitated by the claim amendment time period amended to the independent claim.

Applicant notes that claim 4 was not included in the rejection and therefore the rejection is overcome by incorporating the limits of claim 4 into claim 10. To clarify, claim 4 was not included in the prior rejection, based on the fact that the claim depended on a canceled claim; there was no subject matter in claim 4 that even identified administration of imatinib. However, addition of the time period limitation to independent claim 10 now requires accounting for said limitation, which necessitates the modification to the previous rejection, presented below.

Claim Objections

4. Claim 10 is objected to because of the following informalities: The compound named in the claim is recited with two different names: "N-{5-[4-(4-methyl…" in lines 3-4, but named differently, "N-{5-[4-(4-(4-methyl…" in lines7-8; the second reference

includes non-matching sets of parentheses, which appears to be a typographical error. Appropriate correction is required.

Claim Rejections - 35 USC § 103

5. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

6. Claims 10, 2, 5 and 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Goncharova, et al. ("PI3K is required for proliferation and migration of human pulmonary vascular smooth muscle cells"; 2002 Mar 8; Am. J. Physiol. Lung Cell. Mol. Physiol.; 283: L354-L363; cited in a prior Office Action); Tanabe, et al. ("Mechanical stretch augments PDGF receptor β expression and protein tyrosine phosphorylation in pulmonary artery tissue and smooth muscle cells"; 2000; Molecular and Cellular Biochemistry; 215: 103-113; cited in a prior Office Action); Zimmermann, et al. (WO 99/03854 A1; 1999; IDS 4/21/2005 reference AM); and Dingli, et al. ("Unexplained Pulmonary Hypertension in Chronic Myeloproliferative Disorders"; 2001; Chest; 120 (3): 801-808; cited in a prior Office Action).

This rejection is necessitated by the amendment to claim 10, adding the limitation of exceeding a three month time period to the method.

Goncharova teaches human vascular smooth muscle cell proliferation and migration contribute to vascular remodeling in pulmonary hypertension and atherscerosis; that stimulation of human pulmonary vascular smooth muscle (PVSM) with platelet derived growth factor (PDGF) induced PI3K-dependent activation of Akt, p70 S6 kinase and ribosomal protein S6; and that PDGF-induced proliferation and

migration was inhibited by LY-294002 (a kinase inhibitor; abstract); PDGF appears to be the most potent activator of the PI3K singnaling pathway in many cell types (p. L360, last paragraph); regulation of cell proliferation and motility is a critical step in vascular remodeling, and suggests that targeting PI3K-dependent human PVSM cell motility and proliferation may offer a potential target in blocking development of lesions in atherosclerosis and hypertension (p. L362, last paragraph). Tanabe teaches mechanical stretch of pulmonary artery tissue identified tyrosine phosphorylation proteins that respond to mechanical stress, which included p55 as one of two proteins preferentially phosphorylated by stretch in endothelial cells, corresponding to PDGF receptor β; significant increase in RNA level for PDGF-Rβ was observed in the pulmonary artery of rats with induced pulmonary hypertension, suggesting that stretch-induced overexpression of cell-surface PDGF-Rβ as well as augmentation of tyrosine phosphorylation of proteins might be involved in the mechanotransduction of pulmonary artery (abstract); mechanical stimulus such as stretch induces several responses including smooth muscle contraction, proliferation and apoptosis (p. 103, 1st paragraph); and an inhibitor of tyrosine kinase specifically suppressed the pressure-induced contraction of rat cerebral artery (p. 104, 2nd paragraph).

Neither Goncharova nor Tanabe teach the compounds of the instant claims, nor a method of treating pulmonary hypertension with one of these compounds, nor a time period exceeding three months. Zimmerman teaches the compound of instant formula (I) (imatinib or STI571; abstract) and the monomethanesulfonic acid salt of imatinib (p. 4, figure (II)); phosphorolation of proteins has long been known as an essential step in

the differentiation and division of cells, a process catalyzed by protein kinases, including the tyrosine kinase PDGF receptor; this growth factor plays an important role in normal growth and in pathological cell proliferation, such as in carcinogenesis and in diseases of the smooth-muscle cells of blood vessels, such as in artherosclerosis and thrombosis (p. 9, last 3 paragraphs); the compounds imatinib and its methanesulfonic acid salt are active in inhibition of PDGF receptor kinase and as inhibitors of several kinases (p. 11); the compounds are useful in treatment of cancers and non-malignant diseases, such as artherosclerosis and fibrosis (p. 11, 1st paragraph), and leukemias including chronic myeloid leukemia (p. 11, last paragraph), and diseases with vascular smooth-muscle cell migration and proliferation where PDGR and PDGF-R often play a role, such as restenosis and artherosclerosis; daily dosages include the range of 5-500 mg (p. 17, 1st paragraph), with the specific dosage of 100 mg taught (p. 20, Example 4; p. 21, Example 6).

Dingli teaches a study in which a correlation was observed between pulmonary hypertension and chronic myeloproliferative disorders (that have a propensity to evolve into an acute leukemia, for which imatinib is an established treatment) (abstract; throughout); in characterizing the patients with pulmonary hypertension (PH), most of the patients passed away within a few months or a few years of the time of diagnosis of PH (p. 803, Table 1), the median survival time after diagnosis of PH was 18 months (p. 804, 1st paragraph).

It would have been obvious to one of ordinary skill in the art at the time of the invention to administer an effective dose of imatinib or the monomethanesulfonic acid

salt of imatinib in the treatment of pulmonary hypertension; and to continue this administration for the length pulmonary hypertension is still a condition in the individual, such as the median life time after PH diagnosis, taught by Dingli. The motivation to administer imatinib would have been the following three mechanistic roles for which imatinib is active: 1) both Goncharova and Tanabe implicate the role of PDGF-R in pulmonary hypertension and Zimmerman teaches imatinib is useful in diseases where PDGF-R plays a role; 2) Gocharova teaches cell proliferation and motility is a critical step in vascular remodeling, imatinib inhibits such processes; and 3) Tanabe teaches phosphorylation of PDGF receptor β by stretch in endothelial cells is a component of pulmonary hypertension, such phorsphorylation is inhibited by imatinib. It would not only have been obvious to treat patients with pulmonary hypertension accompanied by pulmonary fibrosis, and also to treat patients before the disease progresses significantly (i.e., before evidence of pulmonary fibrosis is present). The motivation for treating patients early would have been to potentially arrest the progress of the disease so that fibrosis does not occur or is delayed in its onset. It would also have been obvious to treat patients with both primary or secondary pulmonary hypertension with imatinib, considering at least 3 mechanistic reasons existed for such treatment at the time of the invention. It would also have been obvious to administer imatinib for a period exceeding three months, since therapies for conditions such as artherosclerosis or hypertension are routinely continued for time periods in excess of three months, or until the condition remains at normal levels over a period of time on the order of months between visits to a physician.

It is noted that cancer treatments are a use for which tyrosine kinase inhibitors such as imatinib are well known. As pointed out above, Dingli reported a study in which a correlation was observed between pulmonary hypertension and chronic myeloproliferative disorders (that have a propensity to evolve into an acute leukemia, for which imatinib is an established treatment) (abstract; throughout). Although the underlying reasons for this are unknown by Dingli, this study would provided additional motivation for imatinib therapy as treatment for pulmonary hypertension in additional support to the reasons outlined above.

Applicant argues that hindsight is the basis for the present rejection. In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Applicant argues the Examiner has formulated a hypothesis from the prior art that imatinib may have utility for treating pulmonary hypertension; that research in this field is highly unpredictable (demonstrated by the enablement rejection) and the references do not provide any disclosure which would lead the skilled artisan to expect that such a hypothesis will actually turn out to be correct when subject to experimental testing. Certainly it is acknowledged that the state of the art reflects that PAH is a

disease with poor prognosis, more effective treatments need to be developed and unknown triggers contribute to the development of pulmonary hypertension. Nonetheless, the position is maintained that a reasonable expectation of efficacy would be expected for imatinib administration to patients with PH for the reasons: 1) both Goncharova and Tanabe implicate the role of PDGF-R in pulmonary hypertension and Zimmerman teaches imatinib is useful in diseases where PDGF-R plays a role; 2) Gocharova teaches cell proliferation and motility is a critical step in vascular remodeling, imatinib inhibits such processes; and 3) Tanabe teaches phosphorylation of PDGF receptor β by stretch in endothelial cells is a component of pulmonary hypertension, such phorsphorylation is inhibited by imatinib; as well as the supporting observation of the correlation between pulmonary hypertension and chronic myeloproliferative disorders, for which imatinib therapy is commonly used, taught by Dingli. Therefore the rejection is maintained.

Conclusion

7. No claim is allowed.

8. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TIMOTHY P. THOMAS whose telephone number is (571)272-8994. The examiner can normally be reached on Monday-Thursday 6:30 a.m. - 5:00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Timothy P Thomas/
Examiner, Art Unit 1614

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